EXHIBIT H

PATENT
Attorney Docket No. 182.0001-US00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)
Michael FRANCIS, et al.	) Confirmation No. 6860
Application No: 16/152,963	) Group Art Unit: 1613
Filed: October 5, 2018	) Examiner: SONG, Jianfeng
For: BIOPOLYMER COMPOSTIONS, SCAFFOLDS AND DEVICES	) Date: March 15, 2019

AMENDMENT AND RESPONSE TO OFFICE ACTION

Commissioner for Patents
United States Patent and Trademark Office
MAIL STOP: AMENDMENT
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Commissioner:

In response to the Office Action dated January 18, 2019, Applicants respectfully request reconsideration of this application in view of the following amendments and remarks. Please amend this application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS

IN THE CLAIMS:

This listing of claims replaces all prior listings or versions of claims in the present application.

1. (Currently Amended) An implantable scaffold for supporting the repair of a soft tissue injury comprising at least one biopolymer sheet comprising substantially aligned biopolymer fibers,

wherein the biopolymer fibers comprise:

about ~~10 to 50%~~ 20 to 35% by weight of collagen ~~selected from the group consisting of atelocollagen, telocollagen, recombinant human collagen and mixtures thereof~~; and

about ~~50 to 90 %~~ 65 to 80% by weight of a copolymer selected from the group consisting of PLLA, PDLA, PDLLA, PLGA and mixtures thereof; and

wherein the biopolymer fibers have an as-spun average diameter in a range from about 750-4,500 nm.

2. (Cancelled)

3. (Currently Amended) An implantable scaffold of claim ~~2~~ 1, wherein the biopolymer fibers comprise about 27.5 to 32.5% by weight of collagen and about 67.5 to 72.5% by weight of copolymer.

4. (Currently Amended) An implantable scaffold of claim 3, wherein the collagen is ~~Type~~ selected from the group consisting of native, processed, placental and recombinant forms of human, bovine, porcine and marine collagen and the copolymer is ~~high molecular weight~~ PDLLA.

5. (Currently Amended) An implantable scaffold of claim ~~2~~ 4, wherein the collagen is Type 1 collagen and the copolymer is high molecular weight PDLLA.

6. (Previously Presented) An implantable scaffold of claim 5~~1~~, wherein the Type 1 collagen is telocollagen and the copolymer is high molecular weight PDLLA.

7. (Original) An implantable scaffold of claim 1, wherein the biopolymer fibers are treated with a chemical cross-linking reagent.

8. (Original) An implantable scaffold of claim 1, wherein the copolymer is PDLLA having an inherent viscosity of 1.6-2.4 dl/g.

9. (Currently Amended) An implantable scaffold of claim 1, wherein the as-spun average diameter of the biopolymer fibers is in a range from about ~~150-4,500~~ 750 to 2,000 nm.

10. (Currently Amended) An implantable scaffold of claim 9, wherein the as-spun average diameter of the biopolymer fibers is in a range from about ~~400 to 2,000~~ 750 to 1,500 nm.

11. (Currently Amended) An implantable scaffold of claim 10, wherein the as-spun average diameter of the biopolymer fibers is in a range from about 750 to 1,200 nm.

12. (Original) An implantable scaffold of claim 1, wherein the scaffold is vacuum-dried.

13. (Original) An implantable scaffold of claim 1, wherein the biopolymer fibers are annealed biopolymer fibers, mechanically-drawn biopolymer fibers or both annealed and mechanically-drawn biopolymer fibers.

14. (Original) An implantable scaffold of claim 1, wherein the scaffold comprises a single biopolymer sheet.

15. (Original) An implantable scaffold of claim 1, wherein the scaffold comprises a plurality of biopolymer sheets.

16. (Original) An implantable scaffold of claim 1, wherein the scaffold is seeded with cells.

17. (Original) An implantable scaffold of claim 16, wherein the cells are tenocytes.

18. (Original) An implantable scaffold of claim 1, wherein the scaffold after implantation into a host permits host cell and tissue ingrowth and vascularization of the scaffold.

19. (Original) An implantable scaffold of claim 18, wherein after implantation the biopolymer fibers of the scaffold are absorbed and replaced by a host's own tissues.

20. (Original) An implantable scaffold of claim 1, wherein the injured soft tissue is selected from the group of soft tissues comprising tendons and ligaments.

21. (Original) An implantable scaffold of claim 20, wherein the injured soft tissue is a tendon selected from the group consisting of Achilles tendon, rotator cuff tendon, patellar tendon, biceps tendon, and quadriceps tendon.

22. (Original) An implantable scaffold of claim 1, packaged in a sterile container.

23. (Cancelled)

24. (Cancelled)

25. (Cancelled)

26. (Currently Amended) An implantable scaffold for supporting the repair of a soft tissue injury comprising at least one biopolymer sheet comprising substantially aligned biopolymer fibers,

wherein the biopolymer fibers comprise:

about 27.5 to 32.5 % by weight of ~~a~~ Type 1 collagen~~ selected from the group consisting of atelocollagen, telocollagen, recombinant human collagen and mixtures thereof~~; and

about 67.5 to 72.5 % by weight of a copolymer selected from the group consisting of PLLA, PDLA, PDLLA, PLGA and mixtures thereof; and

wherein the as-spun average diameter of the fibers is in a range from about 750 to 1,200 nm.

27. (Currenlty Amended) An implantable scaffold of claim 26, wherein the Type 1 collagen is telocollagen and the copolymer is high molecular weight PDLLA.

28. (Original) An implantable scaffold of claim 26, wherein the fibers of the biopolymer sheet are annealed fibers, mechanically-drawn fibers or both.

29. (Cancelled)

30. (Cancelled)

31. (New) An implantable scaffold of claim 1, having a modulus of elasticity in the range of about 35-750 MPa and a strain to failure of 50 to 200%.

32. (New) An implantable scaffold of claim 6, having a modulus of elasticity in the range of about 35-750 MPa and a strain to failure of 50 to 200%.

33. (New) An implantable scaffold of claim 8, having a modulus of elasticity in the range of about 35-750 MPa and a strain to failure of 50 to 200%.

34. (New) An implantable scaffold of claim 11, having a modulus of elasticity in the range of about 35-750 MPa and a strain to failure of 50 to 200%.

35. (New) An implantable scaffold of claim 13, having a modulus of elasticity in the range of about 35-750 MPa and a strain to failure of 50 to 200%.

36. (New) An implantable scaffold of claim 26, having a modulus of elasticity in the range of about 35-750 MPa and a strain to failure of 50 to 200%.

REMARKS

1. The Status of the Claims

Claims 1, 3-22, 26-28 and 31-36 are pending in this application. Claims 2, 23-25, 29 and 30 have been cancelled. New claims 31-36 have been added. Claims 23-25, 29 and 30 (now cancelled) were withdrawn from consideration in view of the restriction requirement. Claims 1, 3-5, 9-11, 26 and 27 have been amended.

Independent claims 1 and 26 have been amended by deleting the Markush group and now recite Type 1 collagen generally. Dependent claim 27 has also been amended to recite Type 1 collagen. Dependent claims 4 and 5 have been amended to recite Markush groups of certain collagens. Support for these amendments is found on pages 4, 5, 9 and 10 of the as-filed specification. Claim 4 has been amended to recite "PDLLA", not "high molecular weight PDLLA." Claim 5, which depends from claim 4, recites "high molecular weight PDLLA."

Dependent claims 9-10 have been amended to recite the "as-spun" diameters of the biopolymers in the claims implantable scaffold. Support for these amendments is found on page 16 of the specification as originally filed.

New dependent claims 31-36 recite implantable scaffolds having a modulus of elasticity in the range of about 35-750 MPa and a strain to failure of 50 to 200%. Support for new claims 31-36 can be found on page 16 the specification as originally filed.

No prohibited new matter has been added.

2. The Restriction Requirement

The Office has required restriction of the claims of this application under 35 U.S.C. § 121 to one of the following groups:

I. Claims 1-22 and 26-28, drawn to an implantable scaffold; and

II. Claims 23-25, 29 and 30, drawn to a method for facilitation repair of a damaged tendon.

The Office's reasons in support of this restriction requirement are found on pages 2-5 of the Office Action. Applicant appreciates the courtesy of the Examiner's phone call on January 9, 2019 and confirms election of Group I, claims 1-22 and 26-28, without traverse, for examination in this application.

3. The Rejection under 35 U.S.C. § 103

Claims 1-22 and 26-28 are rejected under 35 U.S.C. § 103 as being unpatentable over Qiao et al. ("Composition and in Vitro Evaluation of Nonwoven Type I Collagen/Poly-dl-lactic Acid Scaffolds for Bone Regeneration", J. Funct. Biomater. 2015, 6, 667-686 in view of Francis et al. (US2016002865), Demirbilek et al. ("Oxidative Stress Parameters of L9292 Cells Cultured on Plasma-Modified PDLLA Scaffolds" Appl. Biochem. Biotechnol. (2011) 164:780-792), Chong et al. (US20090202616) and Hossainy et.al. (US201500081000). Applicant respectfully traverses this rejection for the following reasons.

Taking Qiao for what it discloses as a whole, this article relates to a comparison of PDLLA/collagen and PDLLA/gelatine blends with regard to their "wet" stability and the attachment and growth of bone cells on scaffolds contemplated for bone regeneration (Title, Abstract and Conclusions). In contrast, Applicant's claims are directed to scaffolds for the repair of soft tissue injuries (e.g., claim 1) including ligaments and tendons (e.g., claims 20-21). Qiao mentions ligaments only as a source from which to extract collagen.

The Office considers that Qiao, the primary reference, teaches PDLLA blended with Type 1 collagen in ratios of 40:60, 60:40 and 80:20 to produce scaffolds. With respect to these ratios of PDLLA and collagen, Qiao explains at p. 673 that "a massive adverse change in sample geometry was observed in the PDL80 scaffolds, compared with PDL40 and PDL60, with the samples appearing to have shrunk/degraded and folded in on themselves." In contrast, Applicant claims a ratio of 65 to 80% PDLLA (claim 1) and 67.5 to 72.5% PDLLA (claims 3 and 26). Qiao also found that water immersion resulted in loss of fibrous structure in the PDL20 and PDL40 scaffolds, a partial collapse of the scaffold layers in the PDL20 scaffolds and a loss of porosity (Qiao, p. 671). Applicant's invention is based in part on the discovery of surprising biomechanical and biodegradability results from the blended combination of collagen with polylactic acid, including both its L- and D- isoforms, and particularly so with its amorphous mixture referred to as poly-DL-lactide or PDLLA (Spec., p. 11 and 12). **In contrast, Qiao teaches that the use of scaffolds formed with these relatively higher polymer-to-collagen ratios fail because of the described adverse changes in the scaffold material and loss of fibrous structure.**

Qiao also presents data showing that its fibers are **not aligned** (Qiao, p. 6 and Figure 1, as acknowledged by the Office). Regarding fiber diameter, the Office also notes that Qiao's fiber at those three ratios had diameters about 1303 nm, 770 nm and 472 nm, respectively. However, those figures are indicated as measured after incubation rather than "as spun."

The same Table reports that the PDL60 and PDL80 fibers of Qiao have a decreasing mean fiber diameter "as spun" of 668 ± 23.4 nm at PDL60 and 330 ± 13.2 nm at PDL80 (Table 1 at p. 670, see excerpt below).

As-spun fiber diameter: Excerpt from Table 1, p. 670

Composite Scaffolds	Fibre Diameter (nm)	Porosity %
	As-Spun	
PDL20	1686 ± 55.5	70.1 ± 2.43
PDL40	1014 ± 83.4	68.5 ± 1.16
PDL60	668 ± 23.4	65.4 ± 1.42
PDL80	330 ± 13.2	59.5 ± 8.71

In contrast, Applicant claimed implantable scaffold contain aligned biopolymer fibers having an "as-spun" average diameter in a range from about 750-4,500 nm, which is substantially above what Qiao discloses. Moreover, Qiao also explains that the mean fiber diameter decreased with increasing PDLLA content (Qiao, p. 671). **One skilled in the art would not have found Applicant's claimed implantable scaffolds obvious from Qiao's teachings 1) of non-aligned fibers, 2) that higher polymer content fibers fail in performance and 3) that higher polymer content decreases as-spun fiber diameter.**

None of the secondary references teach or suggest that person skilled in the art should ignore Qiao's admonition regarding massive changes in sample geometry and lack of stability with collagen-polymer scaffolds within the ratios of Applicant's claimed blends. The combined references also do not teach or suggest that fibers with Applicant's claimed average as-spun diameters would be achieved with such blends. For example:

- Francis, the secondary reference, does not disclose scaffolds to support the repair of soft tissue injuries. It does disclose aligned fibers, as noted by the Office Action at p. 10, to facilitate cell differention (Francis, Abstract). The reference mentions the use of collagen in a long list of protein types. However, it does not teach blends of collagen and PDLLA in Applicant's claimed range let alone any collagen polymer blends. Where a protein (heart basement membrane or "HBM") is exemplified in a mixture with a polymer (polycaprolactone or "PCL"), their ratio was 90:10 PCL to HBM, which is well beyond the ratio described by Qiao as creating adverse changes in the scaffold material and also is outside the range in Applicant's claims. See also, Qiao at Examples 2 and 3. Moreover, while this reference does disclose fibers in a wide range of

diameters, it does not suggest a collagen fiber blend with the mean diameter of Applicant's claims.

- Demirbilek does not disclose a support for the repair soft tissue or blends of collagen and polymers. It describes the measurement of oxidation-related enzymes and the growth of mouse L929 fibroblasts cultured on PDLLA, polyethylene glycol (PEG), or ethylenediamine (EDA) grafted PDLLA by plasma polymerization. This reference also does not disclose blended fibers or their diameters.

- Chong relates to a two-layer wound dressing having a semi-permeable barrier layer and a scaffold fiber layer formed by electrospinning fibers (Abstract), as distinguished from Applicant's claimed scaffold to support soft tissue repairs. The reference does not describe the repair of soft tissue injuries such as tendons and ligaments. Chong does mention that electrospun fibers can be aligned at [0156] to "rectify" cell and matrix distribution. Where Chong mentions fibers comprising two materials, these are not sheets of aligned, blended fibers as claimed by Applicant, but instead are in the form of a co-axial fiber [0058]. Various proteins and polymers are contemplated, including mixtures ([0052] - [0058]. However, the only blend specifically described was a 50:50 solution of gelatin/TFE and PCL/TFE [0160]. This reference provides no particular motivation to select collagen and does not disclose blends in the ratios claimed by Applicant. Additionally, the reported mean fiber diameter of the Chong blend was 500±120 nm, which also is substantially below the mean diameter claimed by Applicant.

- Hossainy relates to a braided or woven polymeric scaffold deployed on a catheter to support an "anatomical lumen" such as the cavity or duct of a tubular organ found in a blood vessel, urinary tract, and bile duct (Abstract, [0003] and [0143]). Although blends of polymers are disclosed [0125], the reference does not describe scaffolds to support the repair of soft tissue injuries, such as ligaments or tendons, and does not disclose collagen-polymer blends. Hossainy also does not describe collagen-polymer blends or suggest the mean diameter of fibers in the claimed scaffold.

The Office concludes that it would have been obvious to modify Qiao using the aligned fibers and sheets of Francis. Respectfully, Qiao fails to teach the combination of high polymer content and as-spun fiber diameter recited in Applicant's claimed implantable scaffolds. Francis also does not disclose them.

Neither reference teaches or suggests the average as-spun diameters for the recited biopolymer fibers. And none of the other three secondary references fills the gaps in blend ratios or fiber diameters left by the primary and secondary references. Demirbilek does not disclose blended fibers or their diameters. Chong does not provide any motivation to select collagen and does not disclose blends in the ratios or fibers having the diameters as claimed by Applicant. Similarly, Hossainy does not describe collagen-polymer blends or suggest the mean diameter of fibers in Applicant's claimed scaffold. In addition, none of the cited references teach or suggest implantable scaffolds having a modulus of elasticity in the range of about 35-750 MPa and a strain to failure of 50 to 200% as recited in new claims 31-36.

As discussed above, the primary reference Qiao does not teach or suggest Applicants' claim implantable scaffolds. The biopolymers taught by Qiao are different from and fail to achieve the properties and advantages of the biopolymers in Applicants' claimed scaffolds. One of ordinary skill would have been directed away from, not towards, Applicant's claimed invention from the teachings of Qiao. *See, e.g. In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."). For the reasons delineated above none of the secondary references answers the deficiencies of Qiao. One of ordinary skill would not have found the claimed invention obvious from the teachings of the cited references, alone or in combination. Applicants respectfully request this rejection be withdrawn.

4. Conclusion

In view of the above amendments and remarks, Applicants respectfully request further examination of this application and the timely allowance of the pending claims. If the Examiner finds that any issue arises that could be resolved through discussions with Applicants' representative, Applicants invite the Examiner to telephone the undersigned to expedite further prosecution of this application.

Please grant any extensions of time required to enter this response and charge any additional required fees for this submission to our Deposit Account No. 50-5410.

Respectfully submitted,

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